



## Review

# COVID-19: Review on latest available drugs and therapies against SARS-CoV-2. Coagulation and inflammation cross-talking

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## ABSTRACT

SARS-CoV-2 is the agent responsible for COVID-19. The infection can be divided into three phases: mild infection, the pulmonary phase and the inflammatory phase. Treatment options for the pulmonary phase include: Hydroxychloroquine, Remdesivir, Lopinavir/Ritonavir. The inflammatory phase includes therapeutic options like Tocilizumab, Anakinra, Baricitinib, Eculizumab, Emapalumab and Heparin. Human clinical trials are starting to show some results, in some cases like that of Remdesivir and corticosteroids these are controversial. Coagulopathy is a common complication in severe cases, inflammation and coagulation are intertwined and cross-talking between these two responses is known to happen. A possible amplification of this cross-talking is suggested to be implicated in the severe cases that show both a cytokine storm and coagulopathy.

## 1. Introduction

Coronaviruses are enveloped, positive-sense, single stranded RNA viruses that are distributed broadly among humans which cause respiratory, enteric, hepatic, and neurologic diseases (Weiss and Leibowitz, 2011). SARS-CoV-2 is the seventh member of the family of corona viruses that infects humans, after MERS-CoV and SARS-CoV-1, it is a beta coronavirus of group 2B with over 70 % similarity in genetic sequence to SARS-CoV-1 (Hui et al., 2020). Some studies show that angiotensin-converting enzyme 2 (ACE2) is the receptor for SARS-CoV-2 (Cheng and Shan, 2020; Shang et al., 2020). Structural analysis of the spike (S) protein of this new virus showed that its S protein is the one binding to the angiotensin-converting enzyme 2 (ACE2) receptor on human cells (Dong et al., 2020a). The incubation period is generally 3–7 days (within 14 days) (She et al., 2020), mean incubation period is 5.2 days and 97,5% of patients who develop symptoms do so in the first 11,5 days (Li et al., 2020a; Lauer et al., 2020). Symptoms of SARS-CoV-2 infection are nonspecific. The most common ones are onset on fever, weakness and dry cough. Less common symptoms are headache, myalgia, fatigue, oppression in the chest, dyspnea, sputum production,

diarrhea (Wang et al., 2020a), confusion, sore throat, rhinorrhea, chest pain, nausea and vomiting (Chen et al., 2020a). Up to 50 % of patients develop shortness of breath. Acute respiratory distress syndrome (ARDS) is not an uncommon complication when disease cannot be controlled (She et al., 2020). The percentage of patients requiring ARDS treatment is about 10 % for those who are hospitalized and symptomatic. Some patients are known to be asymptomatic carriers of the infection showing no clinical signs (She et al., 2020). Usually severe patients are older and have chronic diseases, among those the most common associated diseases in severe cases are hypertension and cardiovascular diseases (Qin et al., 2020). Total white blood count, lymphocytes, and platelets are lower than the average with extended activated thromboplastin time, increased C-reactive protein and muscle enzyme level. Lymphocytes decrease with diseases progression. Secretion of cytokine, such as IL1B, IL1RA, IL6, IL7, IL8, IL-2R, TNF-alfa, known as cytokine storm, is associated with disease severity (She et al., 2020; Qin et al., 2020; Dong et al., 2020b).

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## 2. Treatment: the pulmonary phase

Here we present the drugs used in each phase. Another possible approach is to discuss every drug related to every phase of viral infection (Adhesion, Entry, Endocytosis, Replication, Protein cleavage, Cytokine Storm, Free circulation) as done in a previous study by the author (Magro, 2020a).

There are basically three phases of infection, the first one is the *mild infection phase* which only requires symptomatic treatment. Patient shows fever, with or without respiratory symptoms, no hypoxemia and negative imaging. This patient needs testing only if there is a high risk of contagion. It is important to perform a 6-minutes walking test before patient discharge to attest there is no exertional hypoxemia.

*Pulmonary phase* is the second phase which requires mostly antiviral treatment. Patient shows fever, bilateral pulmonary consolidations or hypoxemia. This patient needs to be hospitalized. The currently available options include: Hydroxychloroquine/Azithromycin, Remdesivir, Lopinavir/Ritonavir.

### 2.1. Hydroxychloroquine

Hydroxychloroquine alters the process of endocytosis. Hydroxychloroquine is a derivate of chloroquine which alters pH (by increasing it) of endosome and lysosome essential for membrane fusion between host cell and the virus. Due to their basic properties and consequent disruption of cellular vesicle compartments, chloroquine and hydroxychloroquine may also inhibit virion budding and forming of mature virions (Quiros Roldan et al., 2020). An in vitro experiment showed that in chloroquine treated cells endosomes vesicles were abnormally enlarged (Liu et al., 2020). This indicates an altered maturation process of endosomes, blocking endocytosis, resulting in failure of further transport of virions to the replication site (Liu et al., 2020). Hydroxychloroquine is being tested with azithromycin, and the association has shown some result in viral load reduction, but concern about prolonged QT interval arises with the association (Gautret et al., 2020a). Chloroquine and hydroxychloroquine appear to block viral entry into cells not only by inhibition of endosomal acidification, but also by inhibition of glycosylation of host receptors and proteolytic processing, a critical passage of virus-cell ligand recognition. They may also impair the correct maturation and recognition of viral antigens by antigen-presenting cells (APCs) that require endosomal acidification for antigen processing (Quiros Roldan et al., 2020). This could be the explanation as to why they also have immunomodulatory effect through attenuation of cytokine production and inhibition of autophagy and lysosomal activity in host cells (Zhou et al., 2020a; Devaux et al., 2020). Hydroxychloroquine inhibits IL-6, IL-1beta and TNF-alfa release (Quiros Roldan et al., 2020), and it showed also anti-thrombotic properties interfering with platelet aggregation and blood clotting proteins (Quiros Roldan et al., 2020). An open-label nonrandomized study of 36 patients reported improved virologic clearance with hydroxychloroquine. They also reported that the addition of azithromycin to hydroxychloroquine resulted in superior viral clearance in some patients (Gautret et al., 2020a, b). Azithromycin has been shown to be active in vitro against Zika and Ebola viruses (Gautret et al., 2020a; Retallack et al., 2016; Madrid et al., 2015), and to prevent severe respiratory tract infections when administrated to patients suffering from viral infections (Bacharier et al., 2015). Another prospective randomized study of 30 patients showed no benefit and no difference in virologic outcomes between the treated patients versus non treated patients (Chen et al., 2020b). Given the role of iron in several human viral infections, a potential involvement of Hydroxychloroquine in iron homeostasis in SARS-CoV-2 infection has been suggested (Quiros Roldan et al., 2020). Chloroquine and hydroxychloroquine are given orally and are generally well tolerated, however they can cause rare and serious effects such as QTc prolongation, hypoglycemia, neuropsychiatric effects and retinopathy. Known major drug-drug

interactions happen with drugs who are also substrates of CYP2D6 and CYP3A4 (Sanders et al., 2020). A randomized clinical trial of 62 patients from China suffering from COVID-19 showed how hydroxychloroquine shortens time to clinical recovery and absorption of pneumonia (ChiCTR2000029559) (Chen et al., 2020c). One study (NCT04261517, Phase 3) (COVID-19 Clinical Trials, 2020) showed positive preliminary outcomes, even though the sample was small.

### 2.2. Remdesivir

Targeting the RNA-dependent RNA polymerase (RdRp) showed low specificity and low potency, nevertheless the most promising drug belonging to this class is Remdesivir (Li and De Clercq, 2020; Gordon et al., 2020a). Remdesivir is one of the most promising antiviral in fighting SARS-CoV-2. It is an adenosine nucleotide analogue prodrug with broad-spectrum activity against pneumoviruses, filoviruses, paramyxoviruses and coronaviruses (Sheahan et al., 2017). It can inhibit the replication of multiple coronaviruses in respiratory epithelial cells. A recent study showed Remdesivir can compete with natural counterpart ATP. Once it is added to the growing chain, it does not cause an immediate stop but it stops the strand after 3 more nucleotides are added (Gordon et al., 2020a). Remdesivir is currently being tested for antiviral activity against the Ebola virus (Mulangu et al., 2019). Coronaviruses are equipped with exonuclease proofreading enzyme, that makes nucleotide analogues generally a poor therapeutic choice, surprisingly Remdesivir was effective against SARS-CoV-1 and MERS-CoV (Sheahan et al., 2017). Tissue culture studies have shown that Remdesivir is also active against a wide number of highly different coronaviruses including human CoVs, showing a broad-spectrum anti-CoV activity (Brown et al., 2019). Mouse models of SARS-CoV-1 pathogenesis show that early therapy and administration of Remdesivir significantly reduced the presence of the virus in the lungs. Treated animals showed improved clinical signs of disease compared to untreated control animals (Sheahan et al., 2017). Therapeutic and prophylactic use of Remdesivir has recently been tested in nonhuman primate model of MERS-CoV infection. Administration of the drug 24 h prior to inoculation prevented the virus from inducing clinical disease and prevented replication in respiratory tissue, thus preventing lung lesions to form. Therapeutic usage of Remdesivir (12 h after inoculation) showed similar results (de Wit et al., 2020). SARS-CoV-2 RdRp is composed of the nonstructural proteins nsp8 and nsp12. Enzyme kinetics recently showed that this RdRp efficiently incorporates the active triphosphate form of Remdesivir into RNA (Gordon et al., 2020b). Since human safety data are showing promising results (Mulangu et al., 2019), human clinical trials are ongoing. Remdesivir is usually well tolerated, uncommon adverse effects are elevated transaminases and kidney injury; no significant interactions occur with CYP enzymes (Sanders et al., 2020). Intravenous infusion phase 1 clinical trials are showing good safety and pharmacokinetics properties (Sanders et al., 2020). The National Institute of Health is sponsoring a randomized double-blind clinical trial comparing Remdesivir with standard of care (NCT04280705, Phase 3) (COVID-19 Clinical Trials, 2020). Hospitalized patients with advanced COVID-19 and lung involvement who received Remdesivir recovered faster than similar patients who received placebo, according to a preliminary data analysis from this randomized, controlled trial involving 1063 patients. Results are quite controversial between different studies. An example of that is another trial (NCT04257656, Phase 3) of 237 patients, that showed no statistical significant benefits with Remdesivir (Wang et al., 2020b).

### 2.3. Lopinavir/Ritonavir

The Main protease is another suitable drug target, one example in doing so is the combination of Lopinavir/Ritonavir (Li and De Clercq, 2020). Lopinavir/ritonavir is a medication for the human immunodeficiency virus (HIV) used in combination with other

medications to treat adults and children who are infected with HIV-1. Lopinavir in particular is an HIV-1 protease inhibitor, its combination with ritonavir has shown to be effective against SARS-CoV-1 in patients and in tissue culture, via inhibition of 3-chymotrypsin-like protease (3CLpro), the main protease (Chu et al., 2004; de Wilde et al., 2014). The combination of the two also reduced clinical scores and disease progression in animals infected with MERS-CoV (Chan et al., 2015). Previous studies showed the combination of lopinavir and ritonavir to be of some use for SARS-CoV-1 and MERS-CoV infected patients (Yao et al., 2020). Clinical studies in SARS-CoV-1 were associated with reduced mortality and intubation rates (Yao et al., 2020; Chan et al., 2003). Both anti-HIV drugs interacted well with the residues at the active site of SARS-CoV-2 3CLpro. Ritonavir showed a somewhat higher number atomic contacts, a somewhat higher binding efficiency, and higher number of key binding residues compared to lopinavir, which correspond with the slightly lower water accessibility at the 3CLpro active site (Nutho et al., 2020). Adverse effects of Lopinavir/ritonavir include gastrointestinal distress such as nausea and diarrhea, and hepatotoxicity (Sanders et al., 2020). Major drug-drug interactions occur with CYP3A4, CYP2D6, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19 and P-glycoprotein (Sanders et al., 2020). Cao and colleagues reported the results of an open-label randomized clinical trial (ChiCTR2000029308) comparing the efficacy of lopinavir/ritonavir versus standard care in 199 patients with COVID-19. Time to clinical improvement was similar in both groups, no significant differences in viral clearance and in mortality rates were observed (Cao et al., 2020).

### 3. Treatment: the inflammatory phase

*The inflammatory phase* is the third phase, which leads to the most common complication of COVID-19 which is ARDS. Patient shows fever, severe hypoxemia with partial pressure of oxygen (PaO<sub>2</sub>)/fraction of inspired oxygen (FiO<sub>2</sub>) ratio <300 and multiple pulmonary consolidations.

Therapeutic choices include: Tocilizumab and analogues like Sarilumab, Anakinra, Baricitinib, Eculizumab, Emapalumab and Heparin.

#### 3.1. Is Tocilizumab a reasonable choice? Fighting the cytokine storm

SARS-CoV-1, MERS-CoV and SARS-CoV-2 show a relatively higher mortality rates than other coronaviruses and are associated with a cytokine storm, this might suggest that inflammatory responses might play a role in the pathogenesis. If that is the case, targeting the coronavirus alone with antiviral therapy might not be enough to reverse highly pathogenic infections. These observations led to explore the usage of therapies that included type I and II interferons. Interferon beta displayed the best efficacy in reducing MERS-CoV replication in tissue culture (Chan et al., 2013; Hart et al., 2014). A randomized control trial is ongoing in South Arabia (MIRACLE Trial) to determine whether the combination of Lopinavir/Ritonavir and Interferon beta could improve clinical outcomes in MERS-CoV infections (Arabi et al., 2018). In a humanized transgenic mouse MERS-CoV infection model, remdesivir showed more activity and efficacy in prophylactic and therapeutic use than the combination of Lopinavir/Ritonavir and Interferon beta (Sheahan et al., 2020). Triple combination of interferon beta-1b, lopinavir/ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19 is being tested in an open-label, randomized, phase 2 trial (NCT04276688). Early triple antiviral therapy was safe and superior to lopinavir/ritonavir alone in alleviating symptoms and shortening the duration of viral shedding and hospital stay (Hung et al., 2020).

#### 3.2. Tocilizumab and other IL-6 receptor inhibitors

High levels of interleukin 6 (IL-6) and Interleukin 8 (IL-8) were

found in the acute stage associated with lung lesions in SARS-CoV-1 patients. Especially IL-6 can induce the hyper-inflammatory response due to the SARS-CoV-1 invasion of the respiratory tract (Wang et al., 2004). Interestingly, in human epithelial cells, SARS-CoV-1 was able to induce greater IL-6 when compared to influenza A virus (Okabayashi et al., 2006). Although in some murine viral infections IL-6 plays a protective and essential role in the resolution process, in others like in SARS-CoV-1 high levels of IL-6 were associated with severe inflammation and correlated with mortality in the mice (Nagata et al., 2008; Day et al., 2009). This happens also with SARS-CoV-2 in COVID-19 patients: some retrospective and meta-analysis studies show how elevated IL-6 and C-reactive protein (CRP) correlate with mortality and severe disease in comparison to moderate disease (Zhou et al., 2020b; Gong et al., 2020; Coomes and Haghbayan, 2020; Giamarellos-Bourboulis et al., 2020). More evidence suggests that critically ill patients with severe respiratory failure and SARS-CoV-2 have either immune dysregulation or macrophage-activation syndrome, both of which are characterized by pro-inflammatory cytokines. The immune dysregulation, in particular, is driven by the Interleukin-6 (IL-6) and not by Interleukin-1beta (IL-1beta) (Giamarellos-Bourboulis et al., 2020). Interestingly, among all SARS-CoV-1 structural proteins (N, S, E and M), the nucleocapsid protein (N) significantly induced the activation of IL-6 promoter in human airway epithelial cell cultures (Zhang et al., 2007). IL-6 gene expression is activated by the N protein which binds to the NF-κB regulatory element on IL-6 promoter and facilitates its translocation from cytosol to nucleus. The N protein is essential for IL-6 secretion to happen, since deletion of the C-terminus of the N protein resulted in the loss of function in the activation of IL-6 (Zhang et al., 2007). This again points towards excessive activation of the innate immune response. Another proof of that is the damage shown to the pulmonary interstitial arteriolar walls that is more associated with the inflammatory response rather than the pathogenic effect of CoVs (Li et al., 2020b). Since high levels of IL-6 are associated with SARS-CoV-1 and SARS-CoV-2 infections as shown above and since high serum levels of IL-6 have been associated with lung lesions in SARS-CoV-2 patients in the acute and later stages (Wang et al., 2004; Zhou et al., 2020b; Gong et al., 2020; Coomes and Haghbayan, 2020; Giamarellos-Bourboulis et al., 2020; Hsueh et al., 2004), a valid option could be targeting the expression of IL-6 with Tocilizumab a monoclonal antibody against IL-6 Receptor: this option is currently being tested in some patients in Italy with extreme lung injuries (NCT04317092) (COVID-19 Clinical Trials, 2020). This option should be approached only when there are radiological and clinical signs of progression of the lung lesions. Common side effects of Tocilizumab include increase in upper respiratory tract infections, headache, hypertension, hepatotoxicity, infusion related reactions. Major effects include hematologic effects, infections, gastrointestinal perforations and hypersensitivity reactions. Interactions with several CYP450 isoenzymes are described (Sanders et al., 2020). Interestingly, Tocilizumab targets both IL-6 receptor (IL-6R) forms: the soluble one (sIL-6R) and the membrane bound one (mIL-6R). Those two forms seem to work in very divergent ways, since the soluble one is believed to be pro-inflammatory, and the membrane bound IL-6 Receptor is believed to act in an anti-inflammatory way (Rose-John, 2017), inhibiting only the pro-inflammatory one could then be a better option than targeting them both, as suggested in a previous work by the author (Magro, 2020b). Sarilumab, another antibody against IL-6 receptor used in rheumatoid arthritis (Lamb and Deeks, 2018), is being tested in a multicenter, double-blind, clinical phase 2/3 in patients with severe COVID-19 (NCT04315298) (Sanders et al., 2020). Other drugs that showed potential inhibition of IL-6 related JAK/STAT pathway are: Fingolimod which showed to inhibit proliferation and epithelial-mesenchymal transition in sacral chordoma by inactivating IL-6/STAT3 signaling (Wang et al., 2020c), a clinical trial in COVID-19 patients is ongoing (NCT04280588, Phase2) (COVID-19 Clinical Trials, 2020); glatiramer acetate showed potential to downregulate both IL-17 and IL-6 in the central nervous system in an autoimmune encephalitis model

(Begum-Haque et al., 2008).

### 3.3. Canakinumab, Anakinra and Emapalumab

Another option in fighting the cytokine storm is targeting IL-1 with Canakinumab, a monoclonal antibody against IL-1-beta, which is being approved by the Italian drug agency (AIFA) in COVID-19 pneumonia. It is used for the treatment of familial Mediterranean fever and it has been shown to be of use in atherosclerotic diseases for its anti-inflammatory properties (Ozdogan and Ugurlu, 2017; Rothman et al., 2018). A clinical phase 2 trial is ongoing in patients with COVID-19 pneumonia with Canakinumab (NCT04362813) (COVID-19 Clinical Trials, 2020).

Anakinra is also another option in targeting IL-1 Receptor, which is used for rheumatoid arthritis (Ramirez and Canete, 2018). Anakinra is being tested with Tocilizumab in a phase 2 clinical trial (NCT04339712) (COVID-19 Clinical Trials, 2020). It is also being tested in COVID-19 patients combined with Emapalumab (NCT04324021, Phase2/3 multicenter randomized clinical trial) (COVID-19 Clinical Trials, 2020). Emapalumab is a human monoclonal antibody against interferon gamma which acts blocking its binding to cell surface receptors and activation of inflammatory signals, it is used to treat the severe inflammatory condition of hemophagocytic lymphohistiocytosis (HLH) (Al-Salama, 2019).

### 3.4. Gimsilumab

After the SARS-CoV-2 infection, CD4 + T lymphocytes are rapidly activated to become pathogenic T helper (Th) 1 cells and generate Granulocyte-macrophage colony-stimulating factor (GM-CSF). The cytokines environment induces inflammatory CD14<sup>+</sup> CD16<sup>+</sup> monocytes with high expression of IL-6 and accelerates the inflammation (Zhou et al., 2020c). Since IL-6 is not the only responsible of the inflammation, targeting GM-CSF is another possible therapy which has led to the developing and use of anti-GM-CSF antibodies like Gimsilumab (MORAb-022) is an investigational, fully human IgG1 monoclonal antibody being evaluated for its potential in the treatment of multiple inflammatory diseases and cancer. It targets granulocyte-macrophage colony stimulating factor (GM-CSF, CSF2), a growth factor involved in autoimmune diseases, such as rheumatoid arthritis (Kivitz et al., 2016; Senolt, 2019). It is being tested for lung injury or Acute Respiratory Distress Syndrome due to COVID-19, in a phase 2 clinical trial (NCT04351243) (COVID-19 Clinical Trials, 2020).

### 3.5. Coagulation disorder: is heparin the answer?

Is the hyper-inflammatory state the only cause of acute lung injuries? Some studies are starting to show the presence of an associated coagulopathy and, in some cases, antiphospholipid antibodies in patients with COVID-19 who showed multiple infarcts. These patients had evidence of ischemia in the lower limbs, in the hands and bilateral cerebral infarcts in multiple vascular territories (Zhang et al., 2020). These results show a systemic coagulation disorder, but it is possible that the coagulopathy starts in the lungs, and only after it spreads into the other organs. This might suggest that death occurs not only because of the inflammatory response but also because of the local coagulation disorder. Coagulopathy in SARS-CoV-2 infection has been shown to be associated with high mortality, with elevated D-dimer levels and elevated fibrinogen degradation products (FDP) being particularly important markers for the coagulopathy. A comparative analysis between survivors and non-survivors pneumonia patients revealed significantly higher D-dimers, FDP levels, longer PT and APTT compared to survivors on admission; more than 70 % of non survivors met the criteria of disseminated intravascular coagulation (DIC) during hospitalization (Tang et al., 2020a). It has also become clear that COVID-19-related DIC is not a bleeding diathesis but rather a predominantly pro-thrombotic DIC with high venous thromboembolism rates, elevated D-

dimer and fibrinogen levels, low anti-thrombin levels. The use of anticoagulant therapy with heparin showed to decrease mortality (Tang et al., 2020b). This was especially so in patients who meet the sepsis induced coagulopathy (SIC) criteria (a score  $\geq 4$  is required) and in patients with markedly elevated D-dimer (Tang et al., 2020b). This suggests that Low molecular weight heparin (LMWH) at prophylactic dose should be considered in patients meeting SIC criteria and elevated D-dimer. Heparin showed, besides its primary known use, to have also anti-inflammatory properties (Poterucha et al., 2017; Young, 2008; Li, 2008), that could be of therapeutic value in those patients with severe lung inflammation and impaired pulmonary exchange. ARDS is a common complication of COVID-19. Activation of coagulation system has been linked to ARDS onset. It has been shown that the median plasma concentrations of tissue factor and plasminogen activator inhibitor-1 were significantly higher at day seven in patients with ARDS, as compared to non-ARDS (Ozolina et al., 2016). Coagulopathy arises from thrombin generation mediated by localized tissue factor, and depression of fibrinolysis mediated by plasminogen activator in the lungs, in accordance with an increase in plasminogen activator inhibitor-1 (PAI-1) (Ozolina et al., 2016; Glas et al., 2013). This again points towards how heparin might be helpful in fighting this coagulopathy. Another interesting therapeutic property of heparin is its supposed antiviral role (Shukla and Spear, 2001). Heparin showed to inhibit infection in experimental vero cells injected with sputum from a patient with SARS-CoV-1 pneumonia (Vicenzi et al., 2004). Recently, Cui and colleagues, reported the prevalence of venous thromboembolism (VTE) in 81 severe COVID-19 patients with pneumonia admitted in the intensive care unit. The incidence in these patients of VTE (not under thromboprophylaxis) was 25 % and eventually 40 % of them died (Cui et al., 2020). Increased levels of D-Dimer predicted VTE with a sensitivity of 85 %, specificity of 88.5 % and negative predictive value of 94 % (Cui et al., 2020). The prevalence of VTE in ICU patients with COVID-19 pneumonia reported by Cui is higher than the prevalence of VTE associated with other diseases: in a meta-analysis of seven studies including 1783 ICU patients, the mean rate of VTE diagnosis was 12.7, thus suggesting a direct role of COVID-19 in VTE pathogenesis (Malato et al., 2015). Moreover, coagulopathy is known to happen in the majority of patients who die of COVID-19 (Tang et al., 2020a). This suggests that severe COVID-19 patients are at high VTE risk and mortality risk and anticoagulant therapy might improve their prognosis (Kollias et al., 2020). Many mechanisms might contribute to increased VTE risks in COVID-19 patients including: endothelial damage, microvascular thrombosis and occlusion, or even autoimmune mechanism (Zhang et al., 2020). Interestingly, in a recent study of 83 patients, despite the evidence of a progressive COVID-19 coagulopathy over time in some patients, none of those maintained on prophylactic Low-molecular-weight heparin (LMWH) developed systemic DIC. The authors propose also the existence of a pulmonary specific vasculopathy and notice how the ACE2 receptor utilized by SARS-CoV-2 is expressed on both type II pneumocytes and vascular endothelial cells within the lungs, suggesting a possible direct infection and/or damage of those cells by SARS-CoV-2 (Fogarty et al., 2020). Moreover, the cytokine storm associated with COVID-19 could very well be responsible for the thrombin generation and fibrin deposition within the lungs. Interestingly, a recent study showed markedly hypercoagulable thromboelastometry profiles in COVID-19 patients, thus showing how patients with acute respiratory failure may present a severe hypercoagulability rather than a consumptive coagulopathy (Spiezia et al., 2020). Recent statements by the International Society on Thrombosis and Haemostasis (ISTH) and the American Society of Hematology suggest that all hospitalized COVID-19 patients should receive thromboprophylaxis or full therapeutic-intensity anticoagulation (Thachil et al., 2020; COVID-19 and VTE/Anticoagulation, 2020). A Randomized, Open-label Phase 3 Clinical Trial is ongoing to study prevention of COVID-19-associated thrombosis, coagulopathy and mortality with Low- and High-dose anticoagulation with Enoxaparin (NCT04345848) (COVID-19 Clinical Trials,



2020).

### 3.6. Coagulation system and immune system: cross-talking

The activation of both the immune system and the coagulation system is not simply associated in time, but there is extensive crosstalk between the two systems (Choi et al., 2006). Upon injury by a micro-organism, immune cells are recruited and many pro-inflammatory cytokines are secreted, and these cytokines are key mediators of activation of coagulation (Bester et al., 2018). Moreover, inflammation not only leads to activation of coagulation, but coagulation also affects inflammatory activity (Choi et al., 2006). Acute infections can alter hemodynamics, clotting and fibrinolytic systems leading to ischemic events (Libby et al., 2002). This is what might happen with SARS-CoV-2 infection too. High levels of IL-6 and IL-8 have been associated to SARS-CoV-1 and SARS-CoV-2 as already mentioned above, and high levels of these cytokines also correlate with mortality. There is also a clear connection that has been proven between inflammatory events and the development of thrombovascular disease in many clinical scenarios (van Aken et al., 2002). Complications like venous thromboembolism (VTE) has been connected to inflammation and some results showed that patients with VTE have higher plasma levels of interleukin-8 (IL-8) than those without VTE (van Aken et al., 2002; Reitsma and Rosendaal, 2004). Both IL-6 and IL-8 have a role in activation of coagulation, and higher levels of these cytokines may correlate with higher rate of VTE events (van Aken et al., 2002; Reitsma and Rosendaal, 2004), this also might happen in the lungs in patients with severe COVID-19 pneumonia. It has been reported how IL-8 production directly correlates with thrombin-antithrombin (TAT) complex (Johnson et al., 1996). Abnormal clot lysis was observed in the presence of IL-1 beta, IL-6 and IL-8, using thromboelastography. Interestingly, IL-8 shows the most significant results in thromboelastography (TEG) analysis making the clot form faster (hypercoagulation), with an increase in cross-linking fibrin fibers. IL-8 showed also to be able to alter erythrocyte structure and its addition produced a clot with an increased time to clot formation that is less stable and more prone to early lysis (Bester et al., 2018). Thus, the clotting process with increased levels of IL-8 might result in the presence of small thrombi, with an increased risk for vessels occlusion as observed in some COVID-19 patients autopsies (Wichmann et al., 2020). Inflammation stimulates coagulation by leading to intravascular tissue factor expression and down regulation of the fibrinolytic pathway (Esmon et al., 1999). Interestingly, IL-6 is responsible for one of the main mechanism whereby inflammation activates coagulation by inducing tissue factor (TF) expression (Choi et al., 2006; Levi and van der Poll, 2005, 2010). Moreover IL-6 can increase the expression of fibrinogen, factor VIII and vWF, activation of endothelial cells and increase platelets production and reduce the levels of inhibitors of haemostasis such as antithrombin and protein S (Kerr et al., 2001). It has been reported how IL-6 can also elicit a dose-dependent acceleration of thrombus development in arterioles of a WT mice (Senchenkova et al., 2013). IL-6 can also cause the clot to form faster and in a less stable form, and causes a more hypercoagulable clot than IL-1 beta; but IL-8 is still the most potent procoagulant cytokine between those three: causing the most significant changes at all levels of coagulation, including fibrin, thrombin and cellular interactions (Bester and Pretorius, 2016). IL-8 promotes procoagulant activity, also by triggering platelet activation (Regnault et al., 2003). This is evidence of how cytokines and inflammation activate coagulation.

Moreover, activation of coagulation in healthy human subjects by the administration of recombinant factor VIIa also elicits a small but significant increase in the concentrations of IL-6 and IL-8 in plasma (de Jonge et al., 2003). Thrombin too has been shown to have many non-coagulant effects, among these there is IL-6 induction in fibroblasts, epithelial cells and mononuclear cells in vitro (Johnson et al., 1998) and induction of IL-8 production in endothelial cells (Kahn et al., 1999). This is evidence of a well-known cross-talking between inflammations

and coagulation, and of a possible loop mechanism which could be amplified in a setting like that of COVID-19.

### 3.7. Baricitinib

Targeting the *endocytosis* process is also possible with other drugs other than hydroxychloroquine. One known regulator of endocytosis is the AP2-associated protein kinase 1 (AAK1). Using Artificial Intelligence it was possible to find a good inhibitor of AAK1 like Baricitinib, a known Janus kinase inhibitor which can reduce both viral entry and inflammation. It is a selective and powerful JAK-STAT signaling inhibitor thus being effective against the consequences of the elevated levels of cytokines, not only being able of lowering IL-6 levels (Choi et al., 2018), but it also has the potential to inhibit clathrin-mediated endocytosis and thereby inhibit viral infection of cells. It targets members of the numb-associated kinase (NAK) family (AAK1 and GAK), the inhibition of which has been shown to reduce viral infection in vitro (Bekerman et al., 2017). It can be administered orally and has acceptable side effect profile, besides having little interaction with CYP enzymes and drug transporters (Stebbing et al., 2020), since renal elimination is the main clearance mechanism for Baricitinib (Kubo et al., 2019). It regulates innate immunity blocking type-I IFN signal. Baricitinib downregulates CD80/CD86 expression, but not that of HLA-DR in human monocyte-derived dendritic cells in a concentration-dependent manner. Moreover, assessment of the action of Baricitinib on plasmacytoid dendritic cells (pDC), which are the main source of type-I IFN, showed suppressed production of type-I IFN (Kubo et al., 2019). This makes Baricitinib a valid option in every phase of the viral infection, the early stages to reduce viral entry in the cells, and later stages for its anti-inflammatory properties. A Phase2/3 clinical trial is ongoing (NCT04340232) (COVID-19 Clinical Trials, 2020).

### 3.8. Ruxolitinib

Since high levels of IL-6 are the results of excessive inflammatory response, one way to target IL-6 is with antibodies like Tocilizumab, another way is to counteract the response induced by IL-6. This can be done by inhibiting the JAK 1/2 pathway with drugs like Ruxolitinib. Ruxolitinib is a small drug belonging to the class of Janus kinase (JAK) inhibitors and currently clinically used in the treatment of JAK2 mutated myeloproliferative neoplasms, including myelofibrosis and polycythemia vera (Verstovsek et al., 2010; Vannucchi and Harrison, 2017). It shows activity against the JAK2 isoform and also the JAK1 isoform, which play a major role in the signaling pathway of inflammatory cytokines (Mesa, 2010). JAK3 seems to be less sensitive to ruxolitinib (Quintas-Cardama et al., 2010), it also shows anti-inflammatory activity which may be beneficial in its clinical use (Bjorn and Hasselbalch, 2015); it is also implicated in the suppression of the harmful consequences of macrophage activation hemophagocytic lymphohistiocytosis (Maschalidi et al., 2016), which is an under-recognized hyperinflammatory syndrome characterized by fulminant and fatal hypercytokinemia with multi organ failure (Mehta et al., 2020). It has been proven that the expression of major inflammatory cytokines such as TNF alfa and IL-6 was highly reduced in inflammatory human macrophages exposed to ruxolitinib (Bjorn and Hasselbalch, 2015). It has also been shown through an analysis of mRNA expression of cytokines by PCR array that the major inflammatory cytokines, IL-6 and TNF alfa, were highly reduced and down-regulated by Ruxolitinib at both protein and mRNA level (Febvre-James et al., 2018). Ruxolitinib has many effects on many types of cells like Natural Killers (NKs), Dendritic Cells (DCs), and T cells. NKs are usually reduced after Ruxolitinib administration, this happens after NKs maturation is impaired. Ruxolitinib profoundly impairs DCs migration; subsequently, the loss of trafficking DCs may lead to reduced activation of T cells in draining lymph nodes (Elli et al., 2019). Also Treg cells are negatively regulated with Ruxolitinib (Elli et al., 2019). All these results point towards a

**Table 1**  
Summarizes main drugs against SARS-CoV-2 and clinical trials.

Drug	Mechanism of action	Trial/Phase
Hydroxychloroquine (Quiros Roldan et al., 2020; Gautret et al., 2020a; Devaux et al., 2020; Retallack et al., 2016; Bacharier et al., 2015; Chen et al., 2020c; COVID-19 Clinical Trials, 2020)	Inhibition of endosomal acidification, inhibition of glycosylation of host receptors and proteolytic processing (Quiros Roldan et al., 2020). Immunomodulatory effect (Quiros Roldan et al., 2020; Devaux et al., 2020). Iron homeostasis alteration (Quiros Roldan et al., 2020).	NCT04261517, Phase 3 (+)
Remdesivir (Li and De Clercq, 2020; Gordon et al., 2020a; Sheahan et al., 2017; Brown et al., 2019; de Wit et al., 2020; Gordon et al., 2020b; COVID-19 Clinical Trials, 2020; Wang et al., 2020b)	RNA-dependent RNA polymerase inhibition	ChiCTR2000029559 (+) NCT04280705,  Phase 3 (+) NCT04257656, Phase 3(-) ChiCTR2000029308(-)
Lopinavir/Ritonavir (Li and De Clercq, 2020; Chu et al., 2004; de Wilde et al., 2014; Chan et al., 2015; Yao et al., 2020; Nutho et al., 2020; Cao et al., 2020)	Main protease inhibitor	NCT04276688(triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin was superior to lopinavir/ritonavir alone) NCT04317092, Phase 2
Tocilizumab (Sanders et al., 2020; COVID-19 Clinical Trials, 2020; Zhou et al., 2020b; Gong et al., 2020; Coomes and Haghbayan, 2020; Giamarellos-Bourboulis et al., 2020)	IL-6 Receptor Inhibitor	NCT04280588, Phase2 NCT04280588, Phase2
Sarilumab (Lamb and Deeks, 2018; Sanders et al., 2020)	IL-6 Receptor Inhibitor	NCT04362813, Phase2
Fingolimod (Wang et al., 2020c; COVID-19 Clinical Trials, 2020)	inactivating IL-6/STAT3 pathway	NCT04339712,  Phase 2 NCT04324021, Phase2/3 (with Emapalumab) NCT04351243, Phase 2
Canakinumab (Ozdogan and Ugurlu, 2017; Rothman et al., 2018; COVID-19 Clinical Trials, 2020)	monoclonal antibody against IL-1-beta	NCT04345848,
Anakinra (COVID-19 Clinical Trials, 2020; Ramirez and Canete, 2018)	monoclonal antibody against IL-1 Receptor	Phase 3 NCT04340232,  Phase 2/3
Gimsilumab (Zhou et al., 2020c; Kivitz et al., 2016; Senolt, 2019; COVID-19 Clinical Trials, 2020)	monoclonal antibody against GM-CSF	NCT04334044, Phase1/2
Heparin (Tang et al., 2020a, b; Poterucha et al., 2017; Young, 2008; Li, 2008; Fogarty et al., 2020; COVID-19 Clinical Trials, 2020)	anticoagulant, anti-inflammatory (Poterucha et al., 2017; Young, 2008; Li, 2008)	
Baricitinib (Choi et al., 2018; Bekerman et al., 2017; Kubo et al., 2019; COVID-19 Clinical Trials, 2020)	antiviral (Shukla and Spear, 2001; Vicenzi et al., 2004) JAK-STAT signaling inhibitor (Choi et al., 2018)	
Ruxolitinib (Verstovsek et al., 2010; Vannucchi and Harrison, 2017; Mesa, 2010; Elli et al., 2019; COVID-19 Clinical Trials, 2020)	Inhibition of clathrin-mediated endocytosis (Bekerman et al., 2017) Janus kinase (JAK) inhibitor	

possible use of Ruxolitinib as an IL-6 inhibitor like Tocilizumab in the advanced stages of COVID-19, a trial is ongoing(NCT04334044, Phase1/2) (COVID-19 Clinical Trials, 2020).

Table 1 summarizes the main therapeutic options that have been discussed here (Table 1).

#### 4. Other possible drugs

The author discussed the most valid options against COVID-19, but many new alternatives arise every day. Future possible treatments are discussed here. Inhibiting the receptor ACE2 seemed like a reasonable strategy but at the moment is controversial and has shown many possible side effects (Han et al., 2006). Another interestingly choice is to use a recombinant form of the ACE2 receptor to “keep the virus busy” and thus reduce the infected number of cells by inhibiting the first phase of infection, this has particularly been tested in patients with ARDS in the past (Khan et al., 2017). Another option is targeting viral entry: cleavage and activation of SARS-CoV-1 spike protein (S) by a host cell protease is essential for viral entry, this host cell protease is called TMPRSS2. Potential in vitro proven inhibitors are camostat mesylate (Kawase et al., 2012) and K11777 (Zhou et al., 2015), a clinical trial is ongoing for camostat mesylate in COVID-19 patients (NCT04321096 Phase1/2) (COVID-19 Clinical Trials, 2020). Targeting the RNA-dependent RNA polymerase (RDRp) can be done with Favipiravir a drug

belonging to the same class as Remdesivir (Dong et al., 2020b), a clinical trial is ongoing to study Favipiravir against standard of care (NCT04358549, Phase 2) (COVID-19 Clinical Trials, 2020). Targeting the Main protease proteins is what Lopinavir/Ritonavir does (Li and De Clercq, 2020), another recently discovered in vitro protease inhibitor is compound 13-b, which is a modified alfa-ketoamide (Linlin Zhang et al., 2020).

Coagulopathy and inflammatory response are intertwined as already discussed. Both the presence of coagulation dysfunction and the excessive activation of inflammatory response point towards and excessive activation of the complement system. In a murine model lacking C3 and thus unable to activate the common complement pathway, SARS-CoV-1 infection severity was reduced (Gralinski et al., 2018). In a murine model of MERS-CoV infection, increased concentrations of C5a and C5b were found in the serum and in lung tissues (Jiang et al., 2018). This suggests a possible use of Eculizumab, a C5 complement inhibitor, to both prevent coagulation disorder and hyper-inflammation activation (NCT04288713) (COVID-19 Clinical Trials, 2020).

Targeting viral components such as the spike proteins of the virus with specific antibodies is another therapeutic option which is currently being tested (Wang et al., 2020d). Neutralizing Antibodies are active during the free circulation of the virus. Coronaviruses neutralizing antibodies usually target the spike proteins(S) on the viral surface of the virus which allow it to enter host cells. The S protein has two subunits:

**Table 2**  
Summarizes other possible therapeutic compounds in SARS-CoV-2 infection.

Drug	Mechanism of action	Trial/Phase
Recombinant form of the ACE2 (Khan et al., 2017)	Inhibition of viral adhesion to host cells	
Camostat mesylate (Kawase et al., 2012; COVID-19 Clinical Trials, 2020)	Inhibition of viral entry by inhibition of TMPRSS2	NCT04321096 Phase1/2
Favipiravir (COVID-19 Clinical Trials, 2020; Dong et al., 2020b)	RNA-dependent RNA polymerase inhibition	NCT04358549, Phase 2
Eculizumab (Gralinski et al., 2018; COVID-19 Clinical Trials, 2020)	C5 complement inhibitor	NCT04288713
Neutralizing Antibodies (47D11) (Wang et al., 2020d)	Interaction with Spike protein	
Ivermectin (Caly et al., 2020; COVID-19 Clinical Trials, 2020)	Inhibition of in vitro replication	NCT04390022, Phase 2
Corticosteroids: Methylprednisolone (Russell et al., 2020; Wu et al., 2020), Dexamethasone (RECOVERY trial, 2020)	Immunosuppression	NCT04273321, NCT04381936 Phase 2/3

one that mediates cell binding, S1 consisting of 4 domains, and one that mediates cell fusion, the S2 domain. The most neutralizing antibodies are shown to target the receptor interaction site in S1 subunit (Daughtry et al., 2013; Delmar et al., 2015; Dong et al., 2014; Edrington et al., 2011; Eren and van den Berg, 2012; Fang et al., 2015; Widjaja et al., 2019). As shown in previous studies spike proteins of SARS-CoV-2 and SARS-CoV-1 are 77.5 % identical by primary amino acid sequence and structurally very similar (Wrapp et al., 2020; Walls et al., 2020), they bind the ACE2 protein (Li et al., 2003) through the S1 subunit(S1B). The latest developed antibodies showing neutralizing properties is the Human 47D11 antibody, which was shown to target the S1B receptor binding domain of SARS-CoV-1 and SARS-CoV-2. Despite its capacity to inhibit infected cells with SARS-CoV-1 and SARS-CoV-2, the binding activity did not compete with S1B to the ACE2 receptor. This seems to indicate that 47D11 neutralizes SARS-CoV-1 and SARS-CoV-2 through a yet unknown mechanism different from binding interference (Wang et al., 2020d). This study shows how, despite the high capability of the virus to mutate, targeting conserved core structure of the S1B receptor is a good strategy. This provides evidence for the design of the SARS-CoV-2 vaccine composed of viral structural proteins.

Another possible choice is Ivermectin, which showed to inhibit viral replication of SARS-CoV-2 in vitro (Caly et al., 2020), but in vivo studies need to evaluate its effect, clinical trials in COVID-19 are ongoing (NCT04390022, Phase 2).

The use of immunosuppressants like corticosteroids is quite controversial, for some it may be reasonable to counteract the effect of the cytokine storm induced by SARS-CoV-2. Although the recent open label study from Wu and colleagues showed a benefit for corticosteroids (Wu et al., 2020), clinical evidence did not support indistinct use of corticosteroids for SARS-CoV-1 lung injury, as many stated it could result in delayed viral clearance (Russell et al., 2020). Nevertheless, the most promising corticosteroid in SARS-CoV-2 infection is dexamethasone (RECOVERY trial, 2020). Dexamethasone is showing to reduce mortality rates and efficacy especially in critically ill patients (on ventilator support or requiring oxygen therapy). This study enrolled 2104 patients who received a dose of 6 mg per day for 10 days compared to standard of care in 4321 patients. The risk of death was reduced by one-third in the dexamethasone arm in ventilated patients (NCT04381936, Phase 2/3). This evidence suggests we need reconsidering the role of corticosteroid treatment in the SARS-CoV-2 infection.

Table 2 summarizes other therapeutic options that have been discussed here (Table 2).

In conclusions the author showed a list of possible therapies, many are being tested in clinical trials, some still need more testing. This review aimed to give an update on currently available therapies, already known drugs discussed here could have the advantage of speeding up the clinical trial process, since we already known their side effects and tolerability.

#### Declaration of Competing Interest

The author declares no conflict of interest.

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